Phosphorylated CREB binds specifically to the nuclear protein CBP.

Chrivia JC, Kwok RP, Lamb N, Hagiwara M, Montminy MR, Goodman RH.

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Cyclic AMP-regulated gene expression frequently involv a DNA element known as the cAMP-regulated enhancer (CRE). Many transcription factors bind to this element, including the protein CREB, which is activated as a resul of phosphorylation by protein kinase A. This modificatio stimulates interaction with one or more of the general transcription factors or, alternatively, allows recruitment a co-activator. Here we report that CREB phosphorylated by protein kinase A binds specifically to a nuclear protein of M(r) 265K which we term CBP (for CREB-binding protein). Fusion of a heterologous DNA-binding domain t the amino terminus of CBP enables the chimaeric protein to function as a protein kinase A-regulated transcriptional activator. We propose that CBP may participate in cAMP regulated gene expression by interacting with the activate phosphorylated form of CREB.

PMID: 8413673 [PubMed - indexed for MEDLINE]

1: Genes Dev 1994 Apr 15;8(8):869-84 Related Articles, Lin

Molecular cloning and functional analysis of the adenovirus E1A-associated 300-kD protein (p30(reveals a protein with properties of a transcriptional adaptor.

Eckner R, Ewen ME, Newsome D, Gerdes M, DeCapr JA, Lawrence JB, Livingston DM.

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The growth-controlling functions of the adenovirus E1A oncoprotein depend on its ability ot interact with a set of cellular proteins. Among these are the retinoblastoma protein, p107, p130, and p300. We have isolated a cDNA encoding full-length human p300 and mapped the chromosomal location of the gene to chromosome 22q13. p300 contains three cysteine- and histidine-rich regions o which the most carboxy-terminal region interacts specifically with E1A. In its center, p300 contains a bromodomain, a hallmark of certain transcriptional coactivators. We have examined the ability of p300 to overcome the repressive effect of E1A on the SV40 enhancer. We show that p300 molecules lacking an intact E1A-binding site can bypass E1A repression and restore t a significant extent the activity of the SV40 enhancer, eve in the presence of high levels of E1A protein. These resul

imply that p300 may function as a transcriptional adaptor protein for certain complex transcriptional regulatory elements.

PMID: 7523245 [PubMed - indexed for MEDLINE]

1: Nature 1995 Mar 2;374(6517):85-8 Related Articles, Lin

Adenoviral E1A-associated protein p300 as a functional homologue of the transcriptional co-activator CBP.

Lundblad JR, Kwok RP, Laurance ME, Harter ML, Goodman RH.

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The 265K nuclear protein CBP was initially identified as co-activator for the protein kinase A (PKA)-phosphorylated form of the transcription factor CREB. Th domains in CBP that are involved in CREB binding and transcriptional activation are highly related to the adenoviral E1A-associated cellular protein p300 (refs 2, 3 and to two hypothetical proteins from Caenorhabditis elegans, R10E11.1 and K03H1.10 (refs 4 and 5, respectively), whose functions are unknown. Here, we show that CBP and p300 have similar binding affinity for the PKA-phosphorylated form of CREB, and that p300 ca substitute for CBP in potentiating CREB-activated gene expression. We find that E1A binds to CBP through a domain conserved with p300 and represses the CREB-dependent co-activator functions of both CBP and p300. Our results indicate that the gene repression and cell immortalization functions associated with E1A involve th

inactivation of a family of related proteins that normally participate in second-messenger-regulated gene expressio

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- Nature. 1996 Sep 5;383(6595):22-3.

Role of CBP/P300 in nuclear receptor signalling

Chakravarti D, LaMorte VJ, Nelson MC, Nakajima T Schulman IG, Juguilon H, Montminy M, Evans RM.

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The nuclear receptor superfamily includes receptors for steroids, retinoids, thyroid hormone and vitamin D, as we as many related proteins. An important feature of the acti of the lipophilic hormones and vitamins is that the maintenance of homeostatic function requires both intrins positive and negative regulation. Here we provide in vitro and in vivo evidence that identifies the CREB-binding protein (CBP) and its homologue P300 (refs 6,7) as cofactors mediating nuclear-receptor-activated gene transcription. The role of CBP/P300 in the transcriptional response to cyclic AMP, phorbol esters, serum, the lipophilic hormones and as the target of the E1A oncoprotein suggests they may serve as integrators of extracellular and intracellular signalling pathways.

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Phosphorylation of Ser465 and Ser467 in the C terminus of Smad2 mediates interaction with Smad4 and is required for transforming growth factor-beta signaling.

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Members of the Smad family of intracellular signal transducers are essential for transforming growth factor-beta (TGF-beta) to exert its multifunctional effects. After activation of TGF-beta receptors, Smad2 and Smad3 become phosphorylated and form heteromeric complexes with Smad4. Thereafter, these activated Smad complexes translocate to the nucleus, where they may direct transcriptional responses. Here we report that TGF-beta mediates phosphorylation of Smad2 at two serine residues in the C terminus, i.e. Ser465 and Ser467, which are phosphorylated in an obligate order; phosphorylation of Ser465 requires that Ser467 be phosphorylated. Transfection of Smad2 with mutation of Ser465 and/or Ser467 to alanine residues into Mv1Lu cells resulted in dominant-negative inhibition of TGF-beta signaling. These Smad2 mutants were found to stably interact with an activated TGF-beta receptor complex, in contrast to wild-type Smad2, which interacts only transiently. Mutation of Ser465 and Ser467 in Smad2 abrogated complex formation of this mutant with Smad4 and blocked the nuclear accumulation not only of Smad2, but also of Smad4. Thus, heteromeric complex formation of Smad2 with Smad4 is required for nuclear translocation of Smad4. Moreover, peptides from the C terminus of Smad2 containing phosphorylated Ser465 and Ser467 were found to bind Smad4 in vitro, whereas the corresponding unphosphorylated peptides were less effective. Thus, phosphorylated Ser465 and Ser467 in Smad2 may provide a recognition site for interaction with Smad4, and phosphorylation of these sites is a key event in Smad2 activation.

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Partnership between DPC4 and SMAD proteins in TGF-beta signalling pathways.

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The TGF-beta/activin/BMP superfamily of growth factors signals through heteromeric receptor complexes of type I and type II serine/threonine kinase receptors. The signal originated by TGF-beta-like molecules appears to be transduced by a set of evolutionarily conserved proteins known as SMADs, which upon activation directly translocate to the nucleus where they may activate transcription. Five SMAD proteins have so far been characterized in vertebrates. These factors are related to the mediator of decapentaplegic (dpp) signalling, mothers against dpp (Mad), in Drosophila and to the Sma genes from Caenorhabditis elegans. Smad1 and Smad2 have been shown to mimic the effects of BMP and activin, respectively, both in Xenopus and in mammalian cells, whereas Smad3 (a close homologue of Smad2) and the related protein DPC4, a tumour-suppressor gene product, mediate TGF-beta actions. We report here that DPC4 is essential for the function of Smad1 and Smad2 in pathways that signal mesoderm induction and patterning in Xenopus embryos, as well as antimitogenic and transcriptional responses in breast epithelial cells. DPC4 associates with Smad1 in response to BMP and with Smad2 in response to activin or TGF-beta. DPC4 is therefore a regulated partner of SMADs that function in different signalling pathways of the TGF-beta family.

PMID: 8893010 [PubMed - indexed for MEDLINE]